ELSEVIER

Il Farmaco 57 (2002) 341–347

IL FARMACO

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# Influence of processing conditions in the manufacture of O/W creams
# I. Effect on dispersion grade and rheological characteristics

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Received 28 December 2000; accepted 25 August 2001

**Abstract**

Two series of O/W creams having the same general formulation were prepared in three different mechanical conditions (F with an hand blender; S with a turbomixer; T with a vacuum turbo emulsor) using two types of surfactants, polyoxyethylene-cetostearyl alcohols and polyglyceryl-3-methylglucose-distearate. By means of microscopic image analysis it was possible to point out the dispersion grade of the oil internal phase increasing with the energy applied under the conditions of manufacture ($F < S < T$). The level of dispersion influenced significantly on the rheological characteristics of the creams. With polyoxyethylene-cetostearyl alcohols, the viscosity of creams increased as the energy applied in manufacturing increased, with polyglyceryl-3-methylglucose-distearate on the contrary decreased. Moreover, indifferently to the manufacturing conditions, even in the same concentration of surfactant, the creams obtained with the last produced a much greater viscosity. At a parity of manufacturing conditions the differences between the batches of productions were not significant. 

*Keywords:* O/W creams; Polyoxyethylene-cetostearyl alcohols; Polyglyceryl-3-methylglucose-distearate

## 1. Introduction

Many authors, from a long time, studied emulsified systems utilisable in pharmaceutical field for topical drug delivery since they have high patient acceptance.

As it is well known, creams are thermodynamically unstable systems. A reasonable degree of stability over the time can be achieved with the use of appropriate surfactants, co-emulsors and other additives. The type and the quantity of such components, as well as the presence of drugs can influence, even considerably, the system's physical characteristics and consequently its stability [1–5]. Nevertheless manufacture procedures, such as the energy of mixing and hence the level of dispersion, the time of homogenisation, the temperatures of preparation and particularly the 'mode of cooling', may influence the characteristics and the stability of the cream system [4–10].

The energy of mixing and hence the level of dispersion affect the characteristics and stability of an emulsified system. Modifications over time, as a result of the phenomena of flocculation and coalescence, have direct consequences on the stability of the system, as well on the rheological characteristics. The size of the droplets in the dispersed phase of a cream can be ascertained, among the different techniques, by means of a computerised image analysis by optical microscope [11].

The present study was aimed at ascertaining the difference in level of dispersion of the oil phase in different manufactured batches of two O/W creams obtained in three different emulsifying and gelling mechanical conditions.

## 2. Experimental

### 2.1. Materials

2-Octyl dodecanol (Eutanol G); mixture of mono- and diglycerides of palmitic and stearic acids (Cutina

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PII: S0014-827X(02)01213-2

MD); polyoxyethylene-12-cetostearyl alcohol (Eumulgin B1) having HLB 12.0; polyoxyethylene-20-cetostearyl alcohol (Eumulgin B2) having HLB 15.7 were purchased from Henkel Chimica S.p.A. (Lomazzo, Italy). Polyglyceryl-3-methylglucose-distearate (Tego Care 450) having HLB 11.5 was supplied by Goldschmidt Italia (Pandino, Italy). Methylnicotinate was purchased from Sigma–Aldrich. The glycerol and parabens were of pharmaceutical grade.

### 2.2. Manufacture of creams

O/W creams were manufactured with the following two constant w/w% compositions:

(A) Eutanol G 12.5, Cutina MD 10.0, Eumulgin B1 1.5, Eumulgin B2 1.5 (HLB of surfactant mixture 13.85), glycerol 6, methyl-paraben 0.07, propyl-paraben 0.03, water 68.4.

(B) Eutanol G 12.5, Cutina MD 10.0, Tego Care 450 3.0 (HLB = 11.5), glycerol 6, methyl-paraben 0.07, propyl-paraben 0.03, water 68.4.

Being the HLB values of surfactants very narrow, they cannot be considered influencing on creams characteristics.

In each batch of cream was introduced methylnicotinate in 20 mM concentration.

The creams were manufactured in three different mechanical emulsifying conditions:

F batches of 700 g with a Philips hand blender
S batches of 1 kg with a Silverson turbomixer (Crisham, UK)
T batches of 1.5 kg with a Dumek vacuum turbo emulsor (Pianoro, Italy)

For each of the mechanical conditions used, six batches of cream were prepared.

### 2.3. Determination of cream stability by physical techniques

#### 2.3.1. Thermostatation

A Frigostat (Cecchinato, Italy) Thermostat switched on 40 °C was used. The creams were evaluated by visual inspection every 5 days.

#### 2.3.2. Centrifugation

The creams were centrifuged at $6.26 \times 10^3$ *g* in graduated vials. The evaluation of the percentage of the separated aqueous phase was carried out immediately after preparing and after 1, 2, 4, weeks from the preparation.

### 2.4. Determination of rheological characteristics

A Rotovisco RV12 viscosimeter (Haake, Karlsruhe, Germany) with a PG142 programmer was used. Measurements were carried out at shear rates from 0 to 100 $s^{-1}$ in 5 min at temperature of 20 °C, by using MV I measuring equipment.

### 2.5. Image analysis

The size of droplets of dispersed oil phase was calculated on 0.2 g samples of cream spread on a microscope slide and covered. Observations were made using a Laborlux S optical microscope (Leitz, Germany) with $100\times$ lens and $10\times$ eyepiece. This was fitted with a camera interfaced with the *Casti Studio Imaging* software for image analysis transmitted on the monitor. The quantity of at least 500 drops was extracted from each sample of the different batches of cream as delineated on the monitor with the mouse. The data collected were elaborated by the same software in terms of the frequency (%) of size classifications.

## 3. Results

### 3.1. Stability at heating and centrifugation

The batches of the two creams manufactured under different conditions resulted stable after the two common generic tests for checking the stability of an emulsified system (centrifugation at $6.26 \times 10^3$ *g* and heating at 40 °C for 1 month).

### 3.2. Assessment of the level of dispersion of the internal phase of the creams

The size classification and frequency of oil phase droplets were calculated at four different times: 2–4 h after preparation and after 1, 2 and 4 weeks.

In all samples tested, a progressive modification of the frequency curve of droplet size was observed (Fig. 1) both in the case of A formulation (polyoxyethylene-cetostearyl alcohols as surfactant) and B formulation (polyglyceryl-3-methylglucose-distearate as surfactant).

The time course of distribution of size classes of dispersed oil droplets resulted reproducible for the six batches manufactured in each operating condition.

The droplets tended to coalesce, as shown by the progressive increase in the frequency of the greater size classification and the corresponding reduction in the smaller ones.

Between 2 and 4 weeks after preparation, a stabilisation of the level of dispersion of the droplets was observed, while the stabilisation of the internal structure of the systems within the dispersing phase took place.

In all samples tested, the modifications of the level of dispersion of the internal oil phase of the creams were

evidenced by the microscope images of the creams obtained for both the formulations in the three different mechanical conditions after 4 weeks from manufacturing (Fig. 2).

The mechanical conditions for obtaining the cream have shown a significant influence on the size of droplets of dispersed phase. In Fig. 3, the histograms representing the frequency of size classes of dispersed oil droplets in creams tested after 4 weeks from manufacturing are reported.

In the case of creams prepared with polyoxyethylene-cetostearyl alcohols, from the manufacture condition F

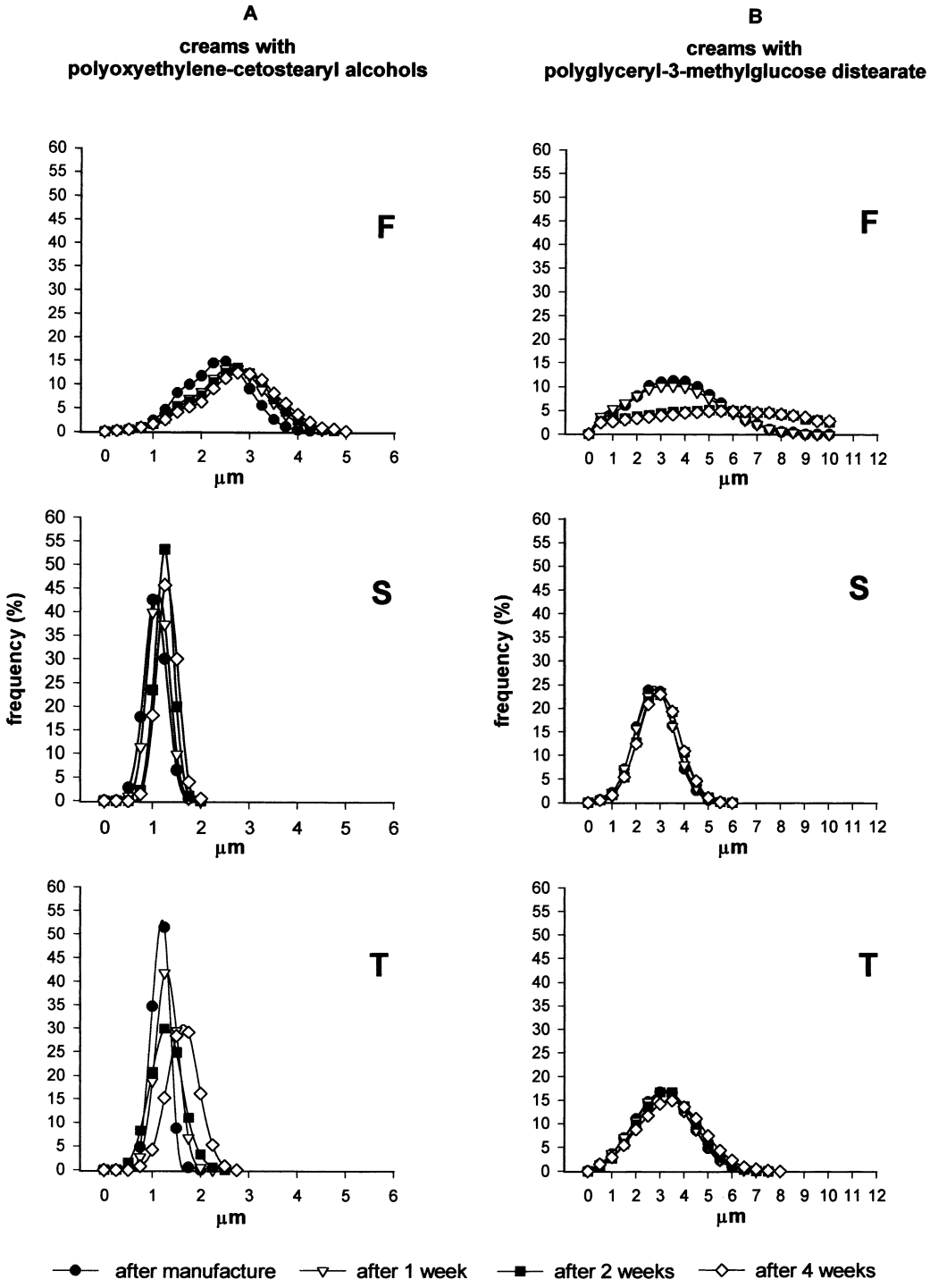


Fig. 1. Variations in distribution curve of frequency (%) droplet size classification of O/W creams obtained with polyoxyethylene-cetostearyl alcohols (A) and with polyglyceryl-3-methylglucose-distearate (B) in time after manufacture. Emulsifying conditions: F, hand blender; S, turbomixer; T, vacuum turbo emulsor.

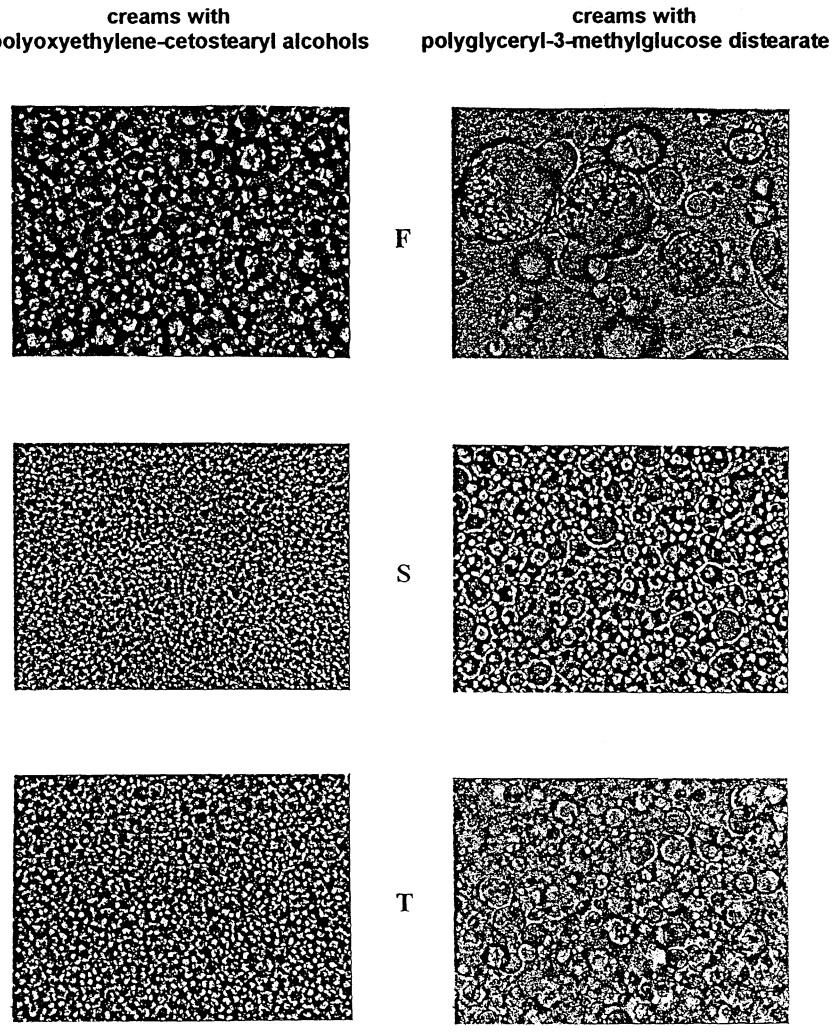


Fig. 2. Images microscopy (1000 ×) of creams contained polyoxyethylene-cetostearyl alcohols (A) and polyglyceryl-3-methylglucose-distearate (B) obtained by different emulsifying conditions: F, hand blender; S, turbomixer; T, vacuum turbo emulsor; checked at 4 weeks after manufacture.

to S, an increase in frequency of size classes of dispersed oil droplets having diameters between 0.8 and 1.6 μm and a contemporary disappearance of the size classes with diameters above 2 μm was observed. By operating in condition T a further increase in frequency of size classes of droplets having diameters between 0.8 and 1.2 μm was obtained.

The creams of B formulation, containing polyglyceryl-3-methylglucose-distearate as surfactant, showed an analogous behaviour as regards the trend of the frequency of size classes of droplets with respect to emulsifying mechanical conditions, even if the diameters of the disperse phase droplets resulted greater. When the operative condition F was adopted, a wide range of size classes of droplets with variable diameters between 2 and 10–20 μm resulted. The number of size classes reduced in the case of the emulsifying conditions S and T, with an increase in frequency of size classes of droplets having diameters between 2 and 4 μm.

By submitting to ANOVA, the values of diameters of disperse oil phase droplets most frequently represented at each of the four time of testing, for the six manufactured batches, differences among batches were non-significant ($P < 0.01$).

### 3.3. Assessment of rheological characteristics

Rheological characteristics of both the creams, having A and B composition, were checked at different time intervals in the course of 4 weeks after manufacture for each of the batches.

In Fig. 4, a comparison of medium relative ($D = 100\ s^{-1}$) viscosity of cream batches, having A and B composition, manufactured under the different emulsifying conditions at different times is reported. In the case of A formulation, containing polyoxyethylene-cetostearyl alcohols as surfactant, the trend of relative viscosity medium values indicate a stabilisation of the internal structure in time course. Viscosity values of the creams manufactured under F condition were lower than those

manufactured under S and T conditions. These last conditions showed analogous viscosity values since 1 week from manufacture. Moreover, those trends indicate that emulsifying and gelling mechanical conditions influenced the structure of the emulsified system.

In the case of B formulation, containing polyglyceryl-3-methylglucose-distearate as surfactant, 1 week after manufacture, independently of the emulsifying condition, an internal stabilisation of the system which remained almost unchanged during the following weeks resulted (Fig. 4). Viscosity medium values, at each check time, were higher in the case of creams manufactured under F condition respect to those under S

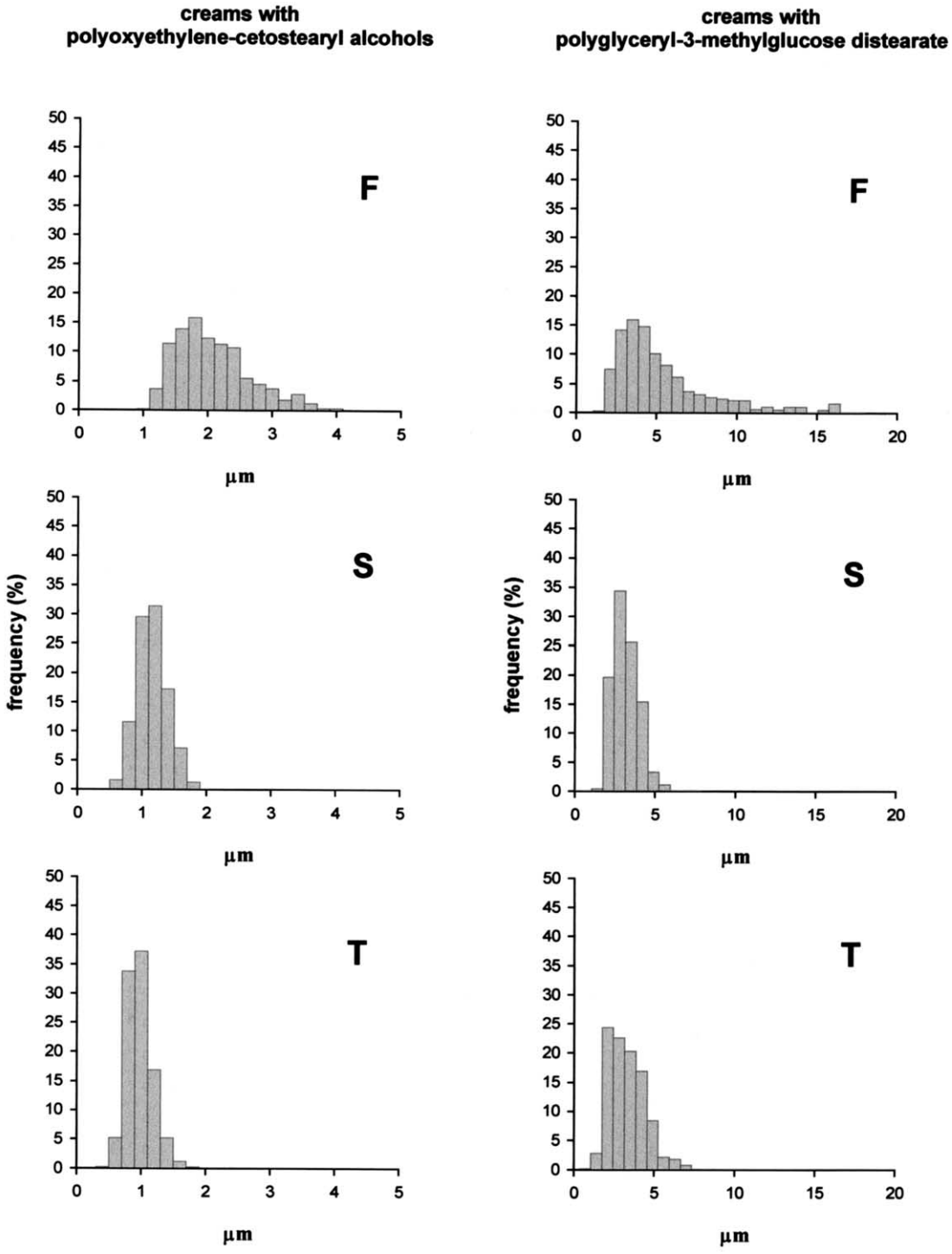


Fig. 3. Histograms representing the frequency of size classes of dispersed oil droplets in creams obtained with polyoxyethylene-cetostearyl alcohols (A) and with polyglyceryl-3-methylglucose-distearate (B).

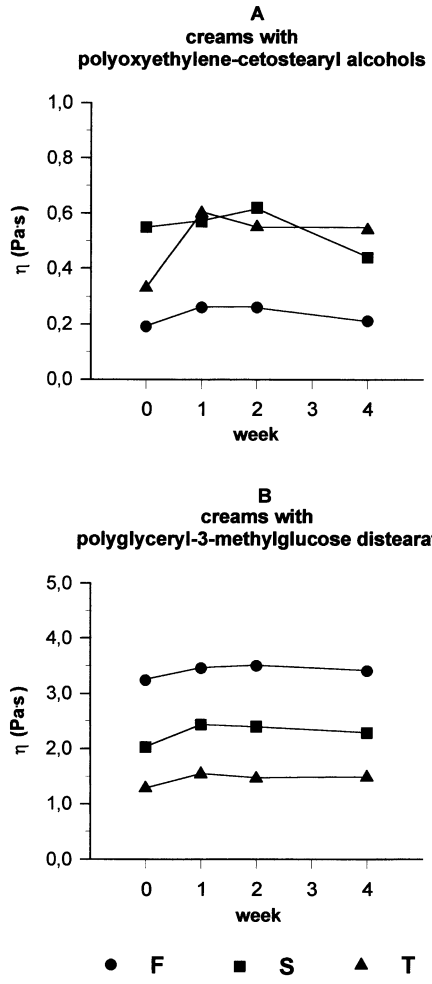


Fig. 4. Comparison of viscosity medium values of cream batches, obtained with polyoxyethylene-cetostearyl alcohols (A) and with polyglyceryl-3-methylglucose-distearate (B), manufactured under the different emulsifying conditions (F, hand blender; S, turbomixer; T, vacuum turbo emulsor) at different times (after manufacture, 1, 2, 4 weeks).

condition. In turn, they showed viscosity medium values higher than obtained under T condition.

Changes in viscosity values were checked among batches, after 4 weeks from manufacture for both formulations A and B (Fig. 5). However, by adopting the same emulsifying condition, changes were comprised in a strict difference from the medium value.

## 4. Discussion

The mechanical conditions for obtaining the cream have shown a significant influence on the size of droplets of dispersed phase (Fig. 3). For both formulations of creams, an increase in the frequency of smaller droplets was observed after increasing the energy applied under the different mechanical conditions of manufacture ($F < S < T$). A progressive variation of distribution in size of oil dispersed phase droplets resulted, independently the adopted emulsifying conditions, for all the tested samples. The course of these variations proceeded in different way according to the surfactant used. In the external aqueous phase, each of the adopted surfactant produce an own lamellar gel structure depending on its chemical structure and concentration, which does not change, however, as a function of the emulsifying conditions. The oil dispersed in droplets, having really different sizes according to manufacturing conditions (F, S, T), but they share in forming the structure of emulsion system and hence in cream viscosity, as a function of their number.

The creams obtained with polyoxyethylene-cetostearyl alcohols (Eumulgin) showed a trend to coalescence immediately after manufacturing, as indicating the progressive decrease in frequency of droplets having higher diameter. In any case, a stabilisation of the level

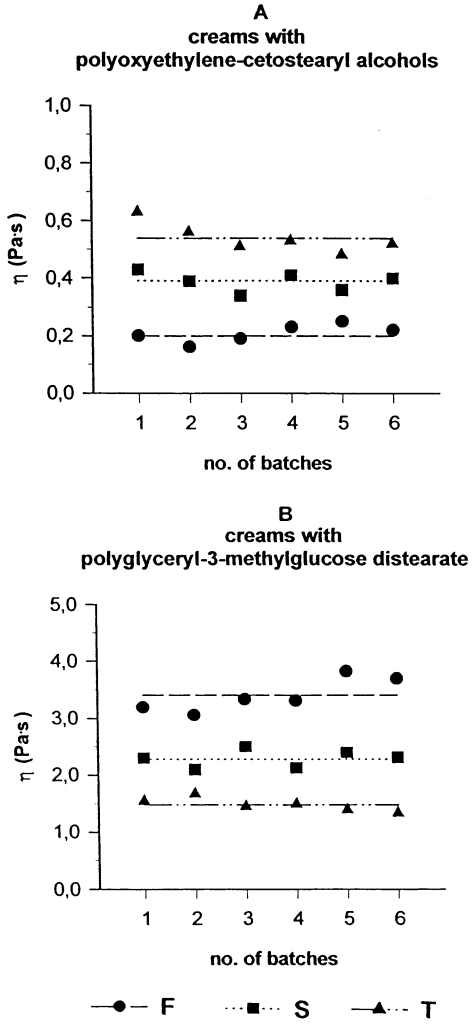


Fig. 5. Comparison of changes in viscosity values of creams, obtained with polyoxyethylene-cetostearyl alcohols (A) and with polyglyceryl-3-methylglucose-distearate (B), checked among batches, after 4 weeks from under the different emulsifying conditions (F, hand blender; S, turbomixer; T, vacuum turbo emulsor).

of dispersion of oil phase and therefore of the internal structure of emulsion between the second and the third week from manufacturing was observed, as the trend of rheological characteristics is demonstrating (Fig. 4).

Polyglyceryl-3-methylglucose-distearate (Tego Care 250) showed to exert a more important influence on physical characteristics of the O/W creams, having the same proportions between the components. Rheological characteristics did not significantly change 1 week after manufacture (Fig. 4). The image analysis revealed the absence of coalescence phenomena for the creams manufactured by a laboratory turbomixer (S condition) and by vacuum turbo emulsor (T condition), confirming the optimal stability of the end product, well shown, however by the rheological behaviour. Creams manufactured by hand blender (F condition), on the rheological point of view, showed to be practically stable just after their preparation in spite of a clear coalescence observed in time by image analysis (see Fig. 1). The viscosity mean values were clearly higher than those prepared under S and T conditions. The microscopy droplets size analysis, however, revealed coarse droplets immediately following preparation. The higher viscosity could be explained by the behaviour suggested by the surfactant manufacturer technical literature [12]. The hydrophilic portions of the surfactant at the droplets surface can mutually bind, holding together the coarse droplets in a structure in which their movement is hindered by the same volume.

In any case, the level of dispersion of the oil phase has shown an important influence on the rheological characteristics of the creams. Mechanical manufacturing conditions gave rise to different viscosities. Nevertheless the viscosity showed a different trend according to the nature of the surfactant. With polyoxyethylene-cetostearyl alcohols the viscosity of creams increased as the energy applied in manufacturing increased, with polyglyceryl-3-methylglucose-distearate on the contrary decreasing. Moreover, indifferently to the manufacturing conditions, even in the same concentration of surfactant, the creams obtained with the last produced a much greater viscosity.

The study allowed to evidence how image analysis could give useful information of the effects produced by a surfactant in stabilising a cream and for the choice of the manufacturing conditions with the aim of achieving the required characteristics of the product and to guarantee an adequate stability.

Moreover, the method allowed to reveal how the technological process of preparation of the creams could have quite a significant influence on the physical characteristics of the product, in particular on the rheological characteristics. At a parity of manufacturing conditions, the differences between the batches of productions were not significant.

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